JC07 Rec'd PCT/PTO 22 MAR 2002

TRANSMITTAL LETTER OT THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371	Attorney Docket No. **8012-1018** U.S. Application No. **10/088965**

INTERNATIONAL APPLN. NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/JP00/05503	**17 AUGUST 2000 (17.08.00)**	

TITLE OF INVENTION: **NOVEL PSEUDOERYTHROMYCIN DERIVATIVES**

APPLICANT(S) FOR DE/EO/US: **SATOSHI OMURA, YUZURU IWAI, TOSHIAKI SUNAZUKA AND TOHRU NAGAMITSU**

Applicant herewith submits to the United States Designated Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☒ This is an express request to begin national examination procedures (35 U.S.C. 371(f)). The submission must include items (5), (6), (9) and (21) indicated below.
4. ☒ The US has been elected by the expiration of 19 months from the priority date (Article 31).
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☒ is attached hereto (required only if not communicated by the International Bureau—***in Japanese language***)
   b. ☐ has been communicated by the International Bureau. See attached PCT/IB/308.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US).
6. ☒ An English language translation of the International Application as filed (35 U.S.C. 371 (c)(2))
   a. ☒ is attached hereto.
   b. ☐ has been previously submitted under 35 U.S.C. 154(d)(4).
7. ☐ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are attached hereto (required only if not communicated by the International Bureau).
   b. ☐ have been communicated by the International Bureau.
   c. ☐ have not been made, however, the time limit for making such amendments has NOT expired.
   d. ☐ have not been made and will not be made.
8. ☐ An English language translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371 (c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ An English language translation of the annexes of the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11 to 20 below concern document(s) or information included:

11. ☒ Information Disclosure Statement (IDS) w/PTO-1449 - ☒ Copy of IDS citations
12. ☐ Assignment Papers (cover sheet & document(s))
13. ☒ A FIRST Preliminary Amendment.
14. ☐ A SECOND or SUBSEQUENT Preliminary Amendment.
15. ☐ A substitute specification.
16. ☐ A change of power of attorney and/or address letter.
17. ☐ A computer-readable form of the sequence listing in accordance with PCT Rule
18. ☐ A second copy of the published international application under 35 U.S.C. 154(d)(4).
19. ☐ A second copy of the English language translation of the international application (35 U.S.C. 154(d)(4)).
20. ☒ Other items or information: **INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT/IPEA/409), INTERNATIONAL SEARCH REPORT (PCT/ISA/210), APPLICATION DATA SHEET, ABSTRACT**

JC13 Rec'd PCT/PTO 22 MAR 2002

U.S. APPLICATION NO. 10/088965	INTERNATIONAL APPLN. NO. PCT/JP00/05503	ATTORNEY DOCKET NO. 8012-1018

21. ☒ The following fees are submitted:	CALCULATIONS PTO USE ONLY	
BASIC NATIONAL FEE (37 CFR 1.492 (a) (1)-(5):		
Neither international preliminary examination fee nor international search fee paid to USPTO and international Search Report not prepared by the EPO or JPO.....$1040.00		
International preliminary examination fee not paid to USPTO but International Search Report prepared by the EPO or JPO.....$890.00		
International preliminary examination fee not paid to USPTO but International search fee paid to USPTO.....$740.00		
International preliminary examination fee paid to USPTO but all claims did not satisfy provision of PCT Article 33 (1)-(4).....$710.00		
International preliminary examination fee paid to USPTO and all claims satisfied provision of PCT Article 33 (1)-(4).....$100.00		
ENTER APPROPRIATE BASIC FEE AMOUNT	$ 890.00	
Surcharge of $130.00 for furnishing the oath or declaration later than ☒ 20- ☐ 30 Months from the earliest claimed priority date (37 CFR 1.492(e))	$ 130.00	

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE		
Total Claims	50 - 20 =	30	X $18.00	$ 540.00	
Independent Claims	5 - 3 =	2	X $84.00	$ 168.00	
MULTIPLE DEPEND CLAIM(S) (if applicable)			+ $280.00	$	
			TOTAL OF ABOVE CALCULATION -	$ **1728.00**	
☐ Applicant claims small entity status. See 37 CFR 1.27. The fees indicated above are reduced by ½.			+	$	
			SUBTOTAL =	$ 1728.00	
Processing fee of $130.00 for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492Z(f)).				$	
			TOTAL NATIONAL FEE =	$ 1728.00	
Fee for recording the enclosed assigned (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) $40.00 per property +				$	
			TOTAL FEES ENCLOSED -	$ 1728.00	
				Amount to be refunded:	$
				Charged:	$

☒ A Check in the amount of **$1,728.00** to cover all fees is attached.

☐ The Commissioner is hereby authorized to charge indicated fees and credit any overpayments to Deposit account No. 25-0120 in the name of Young & Thompson, as described below. A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17.

SEND ALL CORRESPONDENCE TO:
745 South 23rd Street
Arlington, VA 22202
Telephone (703) 521-2297
Y&T Customer No. 000466

TWP/bam
Date: **March 22, 2002**

00466
PATENT .TRADEMARK OFFICE

Thomas W. Perkins
SIGNATURE

Thomas W. Perkins
NAME

33,027
REGISTRATION NO.

PATENT
8012-1018

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of: Satoshi OMURA et al.

Appl. No.: **NEW** Group:

Filed: March 22, 2002 Examiner:

For: NOVEL PSEUDOERYTHROMYCIN DERIVATIVES

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, DC 20231

March 22, 2002

Sir:

The following preliminary amendments and remarks are respectfully submitted in connection with the above-identified application.

IN THE SPECIFICATION:

Please add the following paragraph before the paragraph beginning on page 13, line 8:

--Example 1 is a known compound. This is shown at line 703 in Table 1.—

Please add the following paragraph before the paragraph beginning on page 28, line 22:

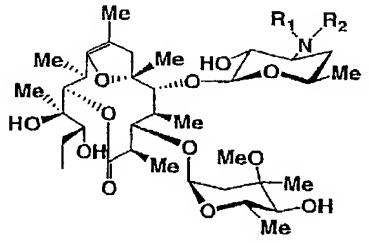
--Example 17 is a known compound. This is shown at line 736 in Table 1.--

IN THE CLAIMS:

Please cancel claims 2 and 21 without prejudice or disclaimer of the subject matter contained therein.

Please amend the claims as follows:

--1.(Amended) A novel pseudoerythromycin derivative represented by the general formula [I],



[I]

wherein R_1 and R_2 are same or different and each represents H, alkyl, alkynyl, acyl, or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl,

wherein R_1 is Me or I-Pr, R_2 is not H.--

REMARKS

Claims 1, 3-20, 22-52 are pending in the present application. Claims 2 and 21 have been cancelled.

Entry of the above amendments is earnestly solicited. An early and favorable first action on the merits is earnestly requested.

Should there be any matters that need to be resolved in the present application, the Examiner is respectfully requested to contact the undersigned at the telephone number listed below.

Attached hereto is a marked-up version of the changes made to the claims by the current amendment. The attached page is captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE."

The Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 25-0120 for any additional fees required under 37 C.F.R. § 1.16 or under 37 C.F.R. § 1.17.

Respectfully submitted,

YOUNG & THOMPSON

Thomas W. Perkins, Reg. No. 33,027
745 South 23rd Street
Arlington, VA 22202
Telephone (703) 521-2297

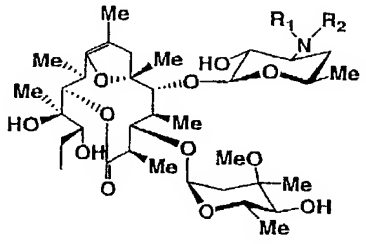
TWP/bam
Attachments

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

The claims have been amended as follows:

1. (Amended) A novel pseudoerythromycin derivative represented by the general formula [I],



[I]

wherein R_1 and R_2 are same or different and each represents H, alkyl, alkynyl, acyl, or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.)

wherein R_1 is Me or I-Pr, R_2 is not H.

3/prts

NOVEL PSEUDOERYTHROMYCIN DERIVATIVES

BACKGROUND OF THE INVENTION

1. Field of the Invention

The present invention relates to novel pseudoerythromycin derivatives or salt thereof.

2. Description of Related Art

Erythromycin (hereinafter sometimes designates as EM) has been used for long time as 14-membered macrolide antibiotic for treatment of infectious disease caused by Gram-positive bacteria. During past ten and several years, erythromycin has known to improve long-term chronic inflammatory diseases such as diffuse panbronchiolitis and bronchial asthma, except for therapeutic action to bacterial infectious diseases. (Kudo, Shoji et al., Studies of clinical results on long term small administration of erythromycin for diffuse panbronchiolitis-Treatment results for 4 years, J. Japan. Thorac. Dis. Assoc., 25: 632-642, 1987).

Erythromycin is an antibiotic and has antibacterial action which is not always required for treatment of inflammatory diseases. Consequently, resistant bacteria are generated in patients who are administered antibiotics, as a result, it causes deterioration for treatment of infectious disease in the other occasion.

As described above, Kudo, Shoji et al. demonstrated that diffuse panbronchiolitis could be improved by long term small administration of erythromycin (Kudo, Shoji et al., Studies of clinical results on long term small administration of

erythromycin for diffuse panbronchiolitis-Treatment results for 4 years, J. Japan. Thorac. Dis. Assoc., 25: 632-642, 1987).

SUMARRY AND OBJECT OF THE INVENTION

Recently, actions other than antibiotic activity of erythromycin is noted, as a result, usefulness other than pulmonary region, for example not limited in diffuse panbronchiolitis but for chronic sinusitis and Crohn's disease are reported. The mechanism of action of erythromycin for chronic disease such as diffuse panbronchiolitis is thought to be the result of original antibacterial action. Research studies are now ongoing, and indicate the antiinflammatory action mediated by immune inflammatory cells in the penumbral chronic respiratory tract inflammation.

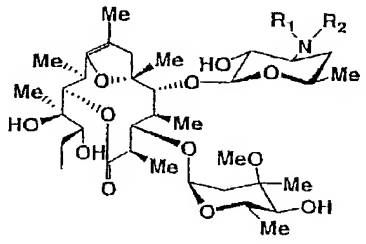
For example, the studies indicate the regulation for migration of neutrophils to infectious region by direct action, and the regulation for migration of neutrophils or for release of active oxygen from neutrophils by indirect action through mediators or cytokines. Further, erythromycin has an action to lymphocytes, macrophages and mast cells to regulate their proliferation or cytokine production, or to induce differentiation. (Kudo, Shoji Ed., Supervisors: Shimizu, Kihachiro and Omura Satoshi "Inflammation, Immunity and Macrolides Up to Date", Iyaku Journal Inc., Osaka, 1996)

As explained above, 14-membered macrolides are thought to cure chronic respiratory diseases as a result of exhibiting immune regulation and antiinflammatory action.

We have aimed at the promoting action of erythromycin for differentiation-induction from monocyte to macrophage (N. Keicho,

S. Kudoh, H. Yotsumoto, K. Akagawa, "Erythromycin promotes monocyte to macrophage differentiation", J. Antibiotics, 47, 80-89, 1994), and tried to synthesize erythromycin derivatives for the purpose of creating the derivatives having disappeared antibacterial action and enhanced promoting action for differentiation-induction.

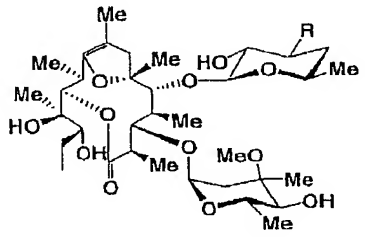
The present invention relates to a novel pseudoerythromycin derivative represented by the general formula [I],



[I]

wherein R_1 and R_2 are same or different and each represents H, alkyl, alkynyl, acyl, or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.

Further, the present invention relates to a novel pseudoerythromycin derivative represented by the general formula [II],

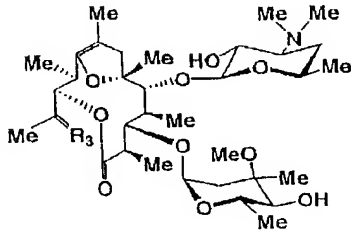


[II]

wherein R is heterocyclic containing N which may optionally have substituents, and Me indicates methyl.

The present invention further relates to a novel pseudo

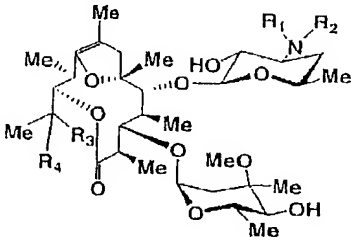
erythromycin derivative represented by the general formula [III],



[III]

wherein R_3 is O or NOH, and Me indicates methyl.

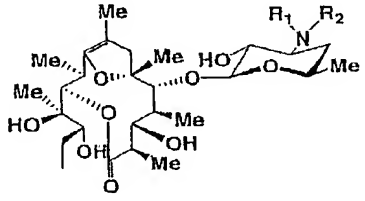
The invention further relates to a novel pseudoerythromycin derivative represented by the general formula [IV],



[IV]

wherein R_1 and R_2 are same or different and each represents H or methyl, R_3 and R_4 represent H, hydroxyl or amino, and Me indicates methyl.

The present invention further relates to a novel pseudo erythromycin derivative represented by the general formula [V],



[V]

wherein R_1 and R_2 are same or different and each represents H or methyl, and Me indicates methyl.

Synthetic methods of various erythromycin derivatives are, for example, illustrated in the synthetic scheme as shown in Fig. 1. Namely, erythromycin A is treated with ice-cold acetic acid according to the references: (a) I. O. Kibwage, R. Busson, G. Janssen, J. Hoogmartens, H. Vanderhaeghe, Translactonization of Erythromycins, J. Org. Chem., 52, 990-996, 1987, (b) H. A. Kirst, J. A. Wind, J. W. Paschal, Synthesis of Ring-Constracted Derivatives of Erythromycin, J. Org. Chem., 52, 4359-4362, 1987, introducing to erythromycin A enol ether (EM 201), subsequently refluxing in methanol with heating in the presence of potassium carbonate to introduce pseudoerythromycin A enol ether (EM701) (known compound).

The product was treated with iodine and sodium acetate according to the reference (L.A. Friberg, U.S. Patent 3,725,385) to obtain de-N-methyl-pseudoerythromycin A enol ether (EM703) (known compound). The compound was further treated with iodine and sodium methoxide to obtain bis(de-N-methyl)-pseudo erythromycin A enol ether (EM721) (novel compound). Alkylation, acylation and sulfonylation using EM703 and EM721 resulted to synthesize various derivatives through bis-de(3'-N-methyl) -3'-N-ethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM722).

The synthetic scheme of compounds of the present invention is illustrated in Fig. 1. Namely, the compounds can be obtained by the synthetic route of: erythromycin A (EMA) → erythromycin A enol ether (EM201) → pseudoerythromycin A enol ether (EM701) → de-N-methyl-pseudoerythromycin A enol ether (EM703) → bis (de-N-methyl)-pseudoerythromycin A enol ether (EM721).

In order to confirm enhancing effect for differentiation

-induction of the compounds of the present invention, the enhancing effect for differentiation-induction from human monocyte to macrophage was assayed. Method is performed as follows.

THP-1 cells were collected from cultured liquid by centrifugation, adjusted the concentration to 2×10^5 cells/ml using medium (RPMI 1640) and distributed into the 48-well plate at 500 μl/well. PMA solution 10 μl and sample solution 5 μl were added in each well, stirred with mild shaking and incubated at 37 ℃ for 72-96 hours under 5% CO_2. Further MTT 0.5 mg/ml solution was added at 300 μl/well, and incubated at 37℃ for 3 hours under 5% CO_2. Supernatant solution was suctioned using the injection tube, added DMSO 500 μl using automatic continuous injector to dissolve formazan completely and transferred each 100 μl to the 96-well plate. The optical absorption was measured using the plate-reader.

Results of the enhancing effect for differentiation -induction from human monocyte to macrophage measured by the above assay method are shown in Table 1.

Table 1

Structure of EM703 analogous derivatives and activities in THP-1/Mϕ system

	Others		Treated conc. (μM)					ED_{50} (μM)*
EM	R_1	R_2	0.3	1	3	10	30	

703	Me	H	+	+	+	+	/	0.3
721	H	H	NT	NT	−	+	/	10
722	Et	H	−	+	+	++	/	1
723	Et	Et	−	+	+		/	1
724	Allyl	H	−	+	+	++	/	1
725	Allyl	Allyl	NT	−	±	+	/	3
726	Ac	H	−	−	−	−	−	−
727	Ms	Me	−	+	+	+	/	1
728	$CH_2C\equiv CH$	H	−	+	+	+	+	1
729	$CH_2C\equiv CH$	$CH_2C\equiv CH$	−	±	±	±	/	1
730	Pr	H	+	+	+	/	/	0.3
731	Pr	Pr	−	−	+	/	/	3
732	Bn	H	+	+	+	÷	/	0.3
733	Bn	Bn	−	±	±	/	/	1
734			−	±	+	+	/	1
735			−	±	+	++	/	1
736	i-Pr	H	−	±	+	++	/	1
737	Me	Me decladinose	NT	NT	−	+	/	10
738	C_6H_{13}	H	−	±	+	/	/	1
739	C_6H_{13}	C_6H_{13}	−	±	+	+	/	1
740	C_2H_4F	Me	±	±	+	+	+	0.3
742	CH_2CN	Me	−	−	−	+	+	10
743	Me	Me C12oxime	NT	−	±	−	/	-
744	C_3H_6OH	Me	NT	−	−	−	/	−
745	C_2H_4OAc	Me	−	−	++	++	++	3

746	Me	Me C12MeCHOH	−	±	+	+	+	1
747			NT	NT	−	±	++	10
748			−	±	++	++	/	1
749	$(CH_2)_{10}Br$	$(CH_2)_{10}Br$	NT	±	+	+	/insolule	1
750	Me	Me C12MeCHNH$_2$	NT	−	−	±	/	10
751	H	Me C12MeCHOH	±	±	+	+	/	0.3
754	Me	H decladinose	NT	−	−	NT	+	30
EM	Me	Ml	NT	−	±	+	+	3
CAM	Me	Ml	NT	NT	−	+	−	10
EM oxim								
	Me	Me C9oxime	NT	−	±	±	++	3

In Table 1: Me: methyl; Pr : propyl; Et: ethyl; Ac: acetyl; and Ms: methanesulfonyl. *ED_{50}: Drug concentration (μ M) required for 50% differentiation-induction of THP in Mϕ.

In Table 1, indicated activity is represented in comparison with enhancing action for differentiation-induction of EM 100 μM, and symbols are: ++: enhanced 100% or more; +: enhanced 50-100%; ±: enhanced 25-50%; -: no activity; /: expressed cytotoxicity; and NT: not tested or under assessment.

As shown in Table 1, since the smaller the value of ED_{50} (μ M) (minimum drug concentration required for 50% differentiation-induction from THP-1 to Mϕ), the stronger the differentiation-induction activity, it was found that the compounds of the present invention have enhancing action for differentiation-induction from THP-1 to Mϕ.

Next, the suppressive effect of the compound of the present invention (EM703) against bleomycin-induced pulmonary fibrosis

was examined (hereinafter sometimes designates bleomycin as BLM).

A sample suspended in 5% gum arabic was orally administered, 50mg/kg/day for 17 days (from day-3 to day-13), and bleomycin, 100mg/kg, was administered from tail vein in day-0. On day-28, animals were sacrificed under anesthesia and fibrosis of the lungs was compared with non-administered mice. Suppressive effects are shown in Table 2.

References:

Azuma A., Furuta T., Enomoto T., Hashimoto Y., Uematsu K., Nukariya N., Murata A., Kudoh S., Preventive effect of erythromycin on experimental bleomycin-induced acute lung injury in rats Thorax 53, 186-189, 1998

Table two

[Administration schedule]

BLM 100 mg/kg

↓

Day -3 -2 -1 0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 28

EM703 50mg/kg/day ↓

sacrificed

Results: Hydroxyproline levels in tissue

Group		Assay result (μmol/l)	Weight conversion (μmol/g)
Cont		440	4.0
BLM	1	785	7.1
BLM	2	733	6.4
EM703	1	552	5.0
EM703	2	489	4.6
EM703	3	591	5.4
BLM+EM703	1	583	5.2
BLM+EM703	2	495	4.5
BLM+EM703	3	437	4.4
BLM+EM703	4	314	2.9
BLM+EM703	5		

Group:

Cont (control) group (n=1)

BLM (bleomycin) group (n=2)

EM (erythromycin) group (n=4)

BLM (bleomycin) + EM (erythromycin) 703 group (n=5)

As indicated above, hydroxyproline is an index of lung fibrosis and higher value indicates hyperfibrosis. Hydroxyproline level, an index for lung injury, in BLM administered group was reduced in a group of BLM+EM703.

Next, the suppressive effect of the compound EM703 against pneumonia caused by influenza viral infection was examined.

Sample was dissolved in physiological saline containing 1% DMSO and amount corresponding to oral dosage of the small administration for long-term therapy was administered from day-1 to day-6 of the infection to mice influenza pneumonia model (0.3 mg and 0.03mg/mice), once a day, intraperitoneally. Results were compared with control group which was given only solvent.

Reference:

Sato K., Suga M., Akaike T. et al., Therapeutic effect of erythromycin on influenza virus-induced lung injury in mice. Am. J. Respir Crit. Care Med. 157, 853-859, 1998.

Results are shown in Fig.2 and Fig.3. In this system, mice developed pneumonia and almost died about 20 days after infection. Contrary to that, as shown in Fig. 2, administration of EM703, 0.3 mg/mice, cured pneumonia and 40% of mice were survived. Further, as shown in Fig. 3, mice without administration of drugs (control) indicated significant decrease of body weight due to pneumonia, but administration of EM703 indicated to increase body weight from day-10. This indicates suppressive effect against pneumonia and result to cure pneumonia.

As described above, the compound of the present invention shows suppressive effect against influenza virus-induced pneumonia.

BRIEF DESCRIPTION OF THE FIGURES

Fig.1 shows an example of the synthetic scheme of the compound of the present invention.

Fig. 2 is a graph of the suppressive effect against pneumonia showing relationship between numbers of day after infection due to influenza virus infection and survival rates of the compound of the present invention.

Fig. 3 is a graph showing suppressive effect of the compound of the present invention on bleomycin-induced pulmonary fibrosis.

DETAILED DESCRIPTION OF PREFERRED EMBODIMENTS

The present invention is explained by illustrating referential examples and examples, but is not limited within these examples.

REFERENTIAL EXAMPLE 1

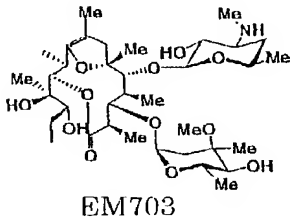
Synthesis of EM701

Glacial acetic acid solution of erythromycin A (12.4 g, 16.9 mmol) was stirred at room temperature for 2 hours, added slowly aqueous sodium hydrogen carbonate and neutralized. The reaction mixture was extracted with chloroform, dehydrated the organic layer with sodium sulfate, filtered off the sodium sulfate and removed the solvent by distillation to obtain crude substance. The crude substance was purified with silica gel chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 →

10 : 1 : 0.05) to obtain EM201 (7.7 g, 63%). Subsequently, potassium carbonate (1.4 g, 10.6 mmol) was added to the methanol solution (100ml) of EM 201 (7.6 g, 10.6 mmol) and refluxed for 2 hours. After distilled off the solvent, the residue was dissolved in aqueous sodium hydrogen carbonate and extracted with chloroform. The mixture was dehydrated with sodium sulfate, filtered and removed the sodium sulfate, then the obtained crude substance was purified by silica gel chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM701 (5.9g, 78%, white powder).

EXAMPLE 1

Synthesis of de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM703)



EM703

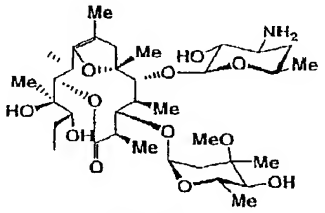
Sodium acetate (3.9 g, 48.5 mmol) and iodine (2.5 g, 9.7 mmol) were added in this order to methanol (52.0 mL)-water (13.0 mL) solution of EM701 (6.9 g, 9.7 mmol) at room temperature, and stirred at 50℃ for 3 hours. During the stirring, 1N aqueous solution of sodium hydroxide was added to maintain at pH 8-9 continuously. After confirming the completion of the reaction by TLC, the reaction mixture was diluted with aqueous ammonia (7.5 mL)-water (200 mL), and extracted with dichloromethane. After dehydrating the organic layer with sodium sulfate, the

sodium sulfate was removed by filtration and distilled off the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM703 (4.8 g, Yield: 70%, white powder).

EM703: m. p. : 177-180℃.

EXAMPLE 2

Synthesis of bis-de(3'-N-methyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal (EM721)



EM721

Sodium (4.5 g, 1.67 mmol) was added in methanol (15 mL) to prepare methanol solution of sodium methoxide, and EM703 (195.4 mg, 0.279 mmol) and iodine (353.6 mg, 1.393 mmol) were added in this order at 0℃ and stirred for 3 hours. After confirming completion of the reaction by TLC, sodium thiosulfate (0.8 g), aqueous ammonia (0.5 mL) and water (80 mL) were added and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM721 (166.3 mg, Yield: 87%, white powder).

EM721 : m. p. : 134-136℃.

IR (KBr) υ : 3467.4, 2973.7, 2935.1, 2879.2, 1700.9, 1637.3, 1457.9, 1380.8, 1265.1, 1166.7, 1126.2, 1079.9, 1037.5, 1016.3 cm^{-1}.

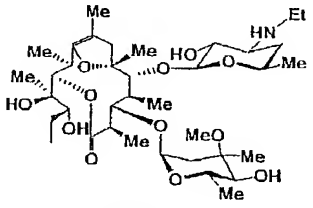
HRMS (FAB)m/z : $C_{35}H_{61}NO_{12}Na$ $[M+Na]^+$

Calculated 710.4091,

Found 710.4060.

EXAMPLE 3

Synthesis of bis-de(3'-N-methyl)-3'-N-ethyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM722)



EM722

N,N-Diisopropylethylamine (26.6 μL, 0.153 mmol) and ethyl iodide (12.2 μL, 0.153 mmol) were added to dimethylformamide (1.0 mL) solution of EM721 (21.0mg, 0.0305 mmol) and stirred at room temperature for 4 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM722 (7.0 mg, Yield: 32%, white powder).

EM722 : m. p. : 124-126℃.

IR (KBr) υ : 3471.6, 2933.2, 1704.8, 1457.9, 1378.9,

1263.1, 1166.7, 1128.2, 1074,2, 1037.5, 1018.2 cm^{-1}.

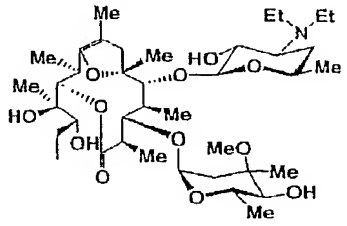
HRMS (FAB)m/z : $C_{37}H_{65}NO_{12}Na$ $[M+Na]^+$

Calculated 738.4404

Found 738.4393.

EXAMPLE 4

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-diethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM723)



EM723

N,N-Diisopropylethylamine (26.6 μL, 0.153 mmol) and ethyl iodide (12.2 μL, 0.153 mmol) were added to dimethylformamide (1.0 mL) solution of EM721 (21.0 mg, 0.0305 mmol) and stirred at room temperature for 4 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM723 (10.3 mg, Yield: 45%, white powder).

EM723 : m. p. : 165-168℃.

IR (KBr) υ : 3473.7, 2935.1, 1699.0, 1382.7, 1317.1, 1267.0, 1166.7, 1126.2, 1108,9, 1078.0,

1016.3 cm^{-1}.

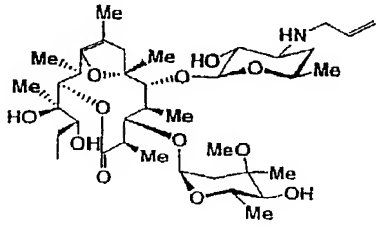
HRMS (FAB)m/z : $C_{39}H_{69}NO_{12}Na$ $[M+Na]^+$

Calculated 766.4717

Found 766.4710.

EXAMPLE 5

Synthesis of bis-de(3'-N-methyl)-3'-N-allyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM724)



EM724

Allyl bromide (148.3 μL, 1.714 mmol) was added to dichloromethane (5.7 mL) solution of EM721 (117.8 mg, 0.171 mmol) and N,N-Diisopropylethylamine (298.6 μL, 1.714 mmol) at 0℃ and stirred at room temperature for 2 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM724 (21.9 mg, Yield: 30%, white powder) was obtained.

EM724 : m. p. : 106-109℃.

IR (KBr) υ : 3448.8, 2971.8, 2933.2, 1718.3, 1637.3, 1380.8, 1265.1, 1166.7, 1126,2, 1078.0,

1037.5, 1016.3 cm^{-1}.

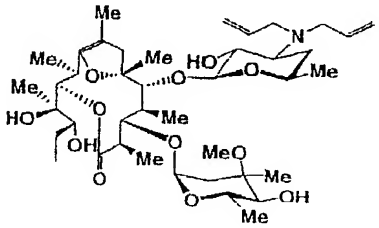
HRMS (FAB)m/z : $C_{38}H_{65}NO_{12}Na$ $[M+Na]^+$

Calculated 750.4404,

Found 750.4420.

EXAMPLE 6

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-diallyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM725)



EM725

Allyl bromide (148.3 μL, 1.714 mmol) was added to dichloromethane (5.7 mL) solution of EM721 (117.8 mg, 0.171 mmol) and N,N-Diisopropylethylamine (298.6 μL, 1.714 mmol) at 0℃, stirred at room temperature for 2 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM725 (64.3 mg, Yield: 59%, white powder).

EM725 : m. p. : 140-142 ℃.

IR (KBr) υ : 3471.7, 2971.8, 2927.4, 1700.9, 1637.3, 1380.8, 1317.1, 1265.1, 1166.7, 1124.3,

1114.7, 1049.1, 1016.3cm^{-1}.

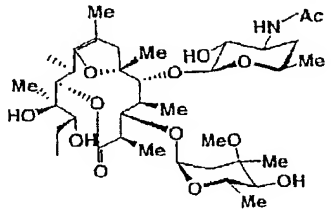
HRMS (FAB)m/z : $C_{41}H_{69}NO_{12}Na$ $[M+Na]^+$

Calculated 790.4717

Found 790.4716.

EXAMPLE 7

Synthesis of bis-de(3'-N-methyl)-3'-N-acetyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM726)



EM726

Acetic anhydride (8.4 μL, 0.0759 mmol) was added to dichloromethane (1.6 mL) solution of EM721 (34.8 mg, 0.0506 mmol) at 0℃, stirred for 10 minutes and further stirred at room temperature for 30 minutes. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, anad removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol = 100 : 1 → 20 : 1) to obtain EM726 (33.4 mg, Yield: 91%, white powder).

EM726 : m. p. : 137-139 ℃.

IR (KBr) υ : 3417.2, 2973.7, 2935.1, 1699.0, 1454.1, 1376.9, 1317.1, 1268.9, 1166,7, 1124.3, 1076.1, 1033.7, 1018.2, 1000.9 cm^{-1}.

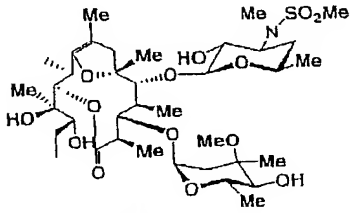
HRMS (FAB)m/z : $C_{37}H_{63}NO_{13}Na$ $[M+Na]^+$

Calculated 752.4197

Found 752.4202.

EXAMPLE 8

Synthesis of de(3'-N-methyl)-3'-N-sulfonyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM727)



EM727

Methanesulfonyl chloride (9.3μL, 0.249 mmol) was added to dichloromethane (4.2 ml) solution of EM703 (87.6 mg, 0.125 mmol) at 0℃ and stirred for 3 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol = 100 : 1 → 20 : 1) to obtain EM727 (37.2 mg, Yield: 91%, white powder).

EM727 : m. p. : 225-228 ℃.

IR (KBr) υ : 3497.6, 2973.7, 2935.1,1704.8, 1463.7, 1380.8, 1326.8, 1319.1, 1265,1, 1166.7, 1141.7, 1074.2, 1041.4,1016.3 cm^{-1}.

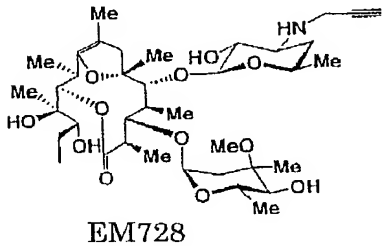
HRMS (FAB)m/z : $C_{37}H_{65}NO_{14}SNa$ $[M+Na]^+$

Calculated 802.4023

Found 802.3995.

EXAMPLE 9

Synthesis of bis-de(3'-N-methyl)-3'-N-propargyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM728)



EM728

3-Bromopropine (137.8 μ L, 1.546 mmol) was added to dichloromethane (5.2 mL) solution of EM721 (106.3 mg, 0.155 mmol) and N,N-Diisopropylethylamine (269.3 μ L, 1.546 mmol), and stirred at room temperature for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1: 0.05) to obtain EM728 (41.3 mg, Yield: 37%, white powder).

EM728 : m. p. : 113-115 ℃.

IR (KBr) υ : 3413.0, 2973.7, 2935.1, 1706.8, 1457.9, 1382.7, 1263.1, 1166.7, 1126,2, 1078.0, 1039.4, 1016.5 cm^{-1}.

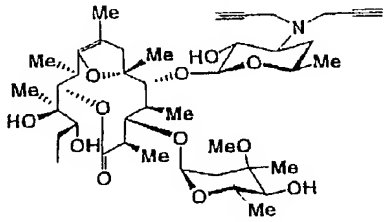
HRMS (FAB)m/z : $C_{38}H_{63}NO_{12}Na$ $[M+Na]^+$

Calculated 748.4248

Found 748.4260.

EXAMPLE 10

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-propargyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM729)



EM729

3-Bromopropine (137.8 μL, 1.546 mmol) was added to dichloromethane (5.2 mL) solution of EM721 (106.3 mg, 0.155 mmol) and N,N-Diisopropylethylamine (269.3 μL, 1.546 mmol) and stirred at room temperature for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1: 0.05) to obtain EM729 (27.9 mg, Yield: 24%, white powder).

EM729 : m. p. : 123-125 ℃.

IR (KBr) υ : 3415.0, 3309.2, 2971.8, 2933.2, 2877.3, 1706.7, 1457.9, 1375.0, 1263.1, 1166.7, 1116.6, 1072.2, 1049.1, 1035.6, 1016.3 cm^{-1}.

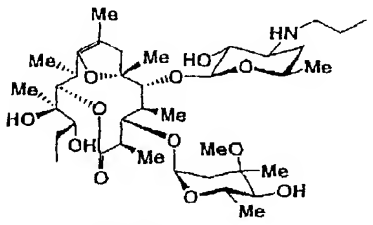
HRMS (FAB)m/z : $C_{41}H_{65}NO_{12}Na$ $[M+Na]^+$

Calculated 786.4404

Found 786.4404.

EXAMPLE 11

Synthesis of bis-de(3'-N-methyl)-3'-N-propyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM730)



EM730

N,N-Diisoproplylethylamine (59.6 μ L, 0.342 mmol) and 1-iodopropane (33.3μL, 0.342 mmol) were added in this order to acetinitrile (2.3 mL) solution of EM721 (23.5 mg, 0.0342 mmol) and refluxed at 80℃ for 20 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM730 (5.7 mg, Yield: 23%, white powder).

EM730 : m. p. : 109-111 ℃.

IR (KBr) υ : 3435.0, 2971.8, 2935.1, 2879.2, 1706.7, 1459.8, 1380.8, 1263.1, 1166.7, 1126.2, 1078.0, 1035.6, 1016.3cm^{-1}.

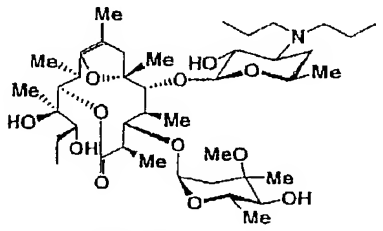
HRMS (FAB)m/z : $C_{38}H_{67}NO_{12}Na$ $[M+Na]^+$

Calculated 752.4560

Found 752.4564.

EXAMPLE 12

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-propyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM731)



EM731

N,N-Diisopropylethylamine (59.6 μ L, 0.342 mmol) and 1-iodopropane (33.3μL, 0.342 mmol) were added in this order to acetinitrile (2.3 mL) solution of EM721 (23.5 mg, 0.0342 mmol) and refluxed at 80℃ for 20 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM731 (12.0 mg, Yield: 40%, white powder).

EM731 : m. p. : 148-151 ℃.

IR (KBr) υ : 3435.0, 2964.1, 2933.2, 2873.4, 1706.7, 1457.9, 1376.9, 1319.1, 1263.1, 1166.7, 1110.8, 1081.9, 1049.1, 1035.6, 1016.3 cm^{-1}.

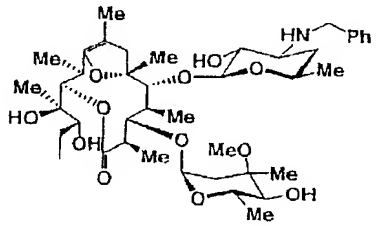
HRMS (FAB)m/z : $C_{41}H_{73}NO_{12}Na$ $[M+Na]^+$

Calculated 794.5030

Found 794.5005.

EXAMPLE 13

Synthesis of bis-de(3'-N-methyl)-3'-N-benzyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM732)



EM732

Benzyl chloride (297.3 μL, 2.584 mmol) was added to dichloromethane (4.3 mL) solution of EM721 (88.8 mg, 0.129 mmol) and N,N-diisopropylethylamine (450.1 μL, 2.584 mmol) at room temperature and stirred for 96 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM732 (49.9 mg, Yield: 50%, white powder).

EM732 : m. p. : 126-128 ℃.

IR (KBr) υ : 3410.0, 2971.8, 2935.1, 1706.7, 1456.0, 1378.9, 1263.1, 1166.7, 1124.3, 1078.0, 1049.1, 1039.4, 1016.3, 983.5, 937.2, 808.0,752.1 cm^{-1}.

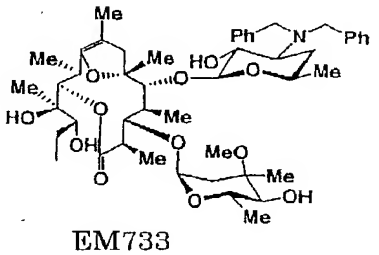
HRMS (FAB)m/z : $C_{42}H_{67}NO_{12}Na$ $[M+Na]^+$

Calculated 800.4560

Found 800.4565.

EXAMPLE 14

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-benzyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM733)



EM733

N,N-Diisopropylethylamine (135.9 μL, 0.780 mmol) and benzyl chloride (89.7 μL, 0.780 mmol) were added in this order to acetinitrile (1.3 mL) solution of EM721 (26.8 mg, 0.0390 mmol) and refluxed at 80℃ for 60 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM733 (19.6 mg, Yield: 58%, white powder).

EM733 : m. p. : 149-152 ℃.

IR (KBr) υ : 3420.6, 2969.8, 2935.1, 1700.9, 1454.1, 1375.0, 1324.9, 1263.1, 1166.7, 1116.6, 1076.1, 1049.1, 1016.3, 752.1, 700.0 cm^{-1}.

HRMS (FAB)m/z : $C_{49}H_{73}NO_{12}Na$ $[M+Na]^+$

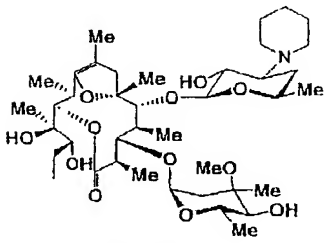
Calculated 890.5030

Found 890.5032

EXAMPLE 15

Synthesis of de(3'-dimethylamino)-3'-piperidino-8, 9-anhydro

-pseudoerythromycin A 6, 9-hemiketal (EM734)



EM734

N,N-Diisopropylethylamine (42.5 μ L, 0.244 mmol) and 1,5-dibromopentane (33.2μL, 0.244 mmol) were added in this order to acetinitrile (4.9 mL) solution of EM721 (16.8 mg, 0.0244 mmol) and refluxed at 80℃ for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM734 (13.3 mg, Yield: 72%, white powder).

EM734 : m. p. : 128-130 ℃.

IR (KBr) υ : 3420.0, 2971.8, 2935.1, 2858.0, 1710.6, 1454.1, 1380.8, 1319.1, 1263.1, 1164.8, 1110.8, 1074.2, 1047.2, 1016.3 cm^{-1}.

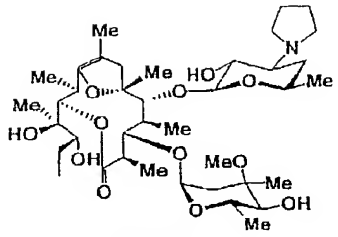
HRMS (FAB)m/z : $C_{40}H_{70}NO_{12}$ $[M+Na]^+$

Calculated 756.4897

Found 756.4901

EXAMPLE 16

Synthesis of de(3'-dimethylamino)-3'-pyrrolidino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM735)



EM735

N,N-diisopropylethylamine (40.2 μ L, 0.231 mmol) and 1,4-dibromobutane (27.6μL, 0.231 mmol) were added in this order to acetinitrile (4.6 mL) solution of EM721 (15.9 mg, 0.0231 mmol) and refluxed at 80℃ for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 1 : 0.1) to obtain EM735 (11.9 mg, Yield: 70%, white powder).

EM735 : m. p. : 127-129 ℃.

IR (KBr) υ : 3420.0, 2971.8, 2937.1, 1702.8, 1457.9, 1382.7, 1265.1 1166.7, 1124.3, 10761.1, 1049.1, 1016.3 cm^{-1}.

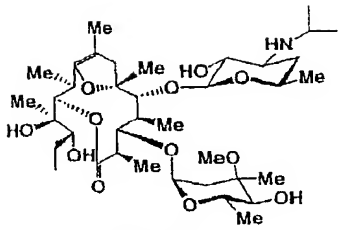
HRMS (FAB)m/z : $C_{39}H_{68}NO_{12}$ $[M+Na]^+$

Calculated 742.4741

Found 742.4743

EXAMPLE 17

Synthesis of bis-de(3'-N-methyl)-3'-N-(2-propyl)-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM736)



EM736

N,N-Diisopropylethylamine (459.2 μ L, 2.636 mmol) and 2-bromopropane (247.5μL, 2.636 mmol) were added in this order to acetinitrile (4.4 mL) solution of EM721 (90.6 mg, 0.132 mmol) and stirred at 80℃ for 72 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 1 : 0.1) to obtain EM736 (25.3 mg, Yield: 26%, white powder). The raw material EM721 was recovered 47.1 mg (Yield: 52%).

EM736 : m. p. : 102-104 ℃.

IR (KBr) υ : 3420.0, 2971.8, 2933.2, 2877.3, 1718.3, 1459.8, 1380.8, 1263.1, 1166.7, 1126.2, 1078.0, 1049.1, 1016.3cm^{-1}.

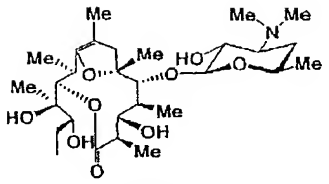
HRMS (FAB)m/z : $C_{38}H_{67}NO_{12}Na$ $[M+Na]^+$

Calculated 752.4560

Found 752.4576.

EXAMPLE 18

Synthesis of de(3-O-cladinosyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal (EM737)



EM737

p-toluenesulfonic acid monohydrate (80.3 μL, 0.422 mmol) was added to dimethylformamide (5.6 mL) solution of EM701 (201.6 mg, 0.282 mmol) and stirred at 50℃ for 8 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water, adjusted to pH 8.0 by adding saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM737 (84.7 mg, Yield: 54%, white powder).

EM737 : m. p. : 109-111 ℃.

IR (KBr) υ : 3486.7, 2973.7, 2937.1, 2877.3, 1708.6, 1631.5, 1457.9, 1382.7, 1265.1, 1164.8, 1110.8, 1076.1, 1039.4 cm^{-1}.

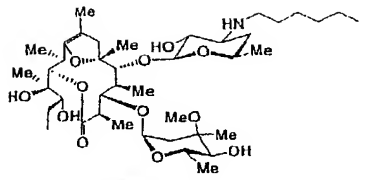
HRMS (FAB)m/z : $C_{29}H_{52}NO_9$ $[M+Na]^+$

Calculated 558.3641

Found 558.3616

EXAMPLE 19

Synthesis of bis-de(3'-N-methyl)-3'-N-hexyl-8, 9-anhydro -pseudoerythromycin A 6, 9-hemiketal (EM738)



EM738

N,N-Diisopropylethylamine (408.5 μL, 2.345 mmol) and 1-bromohexane (328.7μL, 2.345 mmol) were added in this order to acetinitrile (3.9 mL) solution of EM721 (80.6 mg, 0.117 mmol) and stirred at 60℃ for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM738 (33.7 mg, Yield: 45%, white powder). The raw material EM721 was recovered 24.6 mg (Yield: 31%).

EM738 : m. p. : 115-118 ℃.

IR (KBr) υ : 3430.3, 2969.8, 2933.2, 2858.0, 1712.5, 1459.8, 1378.9, 1317.1, 1263.1, 1166.7, 1126.2, 1078.0, 1047.2, 1039.4, 1016.3 cm^{-1}.

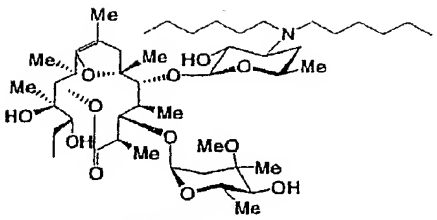
HRMS (FAB)m/z : $C_{41}H_{74}NO_{12}$ $[M+Na]^+$

Calculated 772.5210

Found 772.5214.

EXAMPLE 20

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-dihexyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM739)



EM739

N,N-Diisopropylethylamine (116.0 μL, 0.666 mmol) and 1-bromohexane (93.6 μL, 0.666 mmol) were added in this order to acetinitrile (1.1 mL) solution of EM721 (22.9 mg, 0.0333 mmol) and stirred at 60℃ for 72 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM739 (20.1 mg, Yield: 71%, white powder).

EM739 : m. p. : 158-160 ℃.

IR (KBr) υ : 3490.0, 2958.3, 2931.3, 2871.5, 2858.0, 1702.8, 1459.8, 1376.9, 1319.1, 1265.1, 1166.7, 1126.2, 1083.8, 1016.3 cm^{-1}.

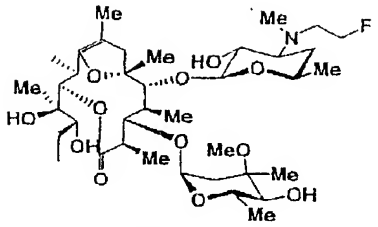
HRMS (FAB)m/z : $C_{47}H_{86}NO_{12}$ $[M+H]^+$

Calculated 856.6149

Found 856.6132.

EXAMPLE 21

Synthesis of bis-de(3'-N-methyl)-3'-N-(2-fluoroethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM740)



EM740

N,N-Diisopropylethylamine (347.7 μL, 1.996 mmol) and 1-bromo-2-fluoroethane (148.6 μL, 1.996 mmol) were added to dimethylformamide (3.3 mL) solution of EM703 (70.0 mg, 0.0998 mmol) at room temperature and stirred for 48 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM740 (36.0 mg, Yield: 48%, white powder). The raw material EM703 was recovered 25.5 mg (Yield: 36%).

EM740 : m. p. : 138-140 ℃.

IR (KBr) υ : 3480.8, 2973.7, 2937.1, 2879.2, 1704.8, 1457.9, 1376.9, 1319.1, 1265.1, 1166.7, 1126.2, 1114.7, 1076.1, 1049.1, 1035.6, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{38}H_{66}NO_{12}Fna$ $[M+Na]^+$

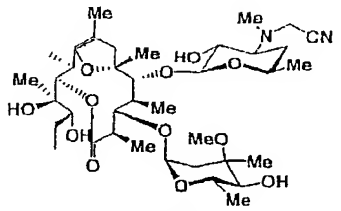
Calculated 770.4467

Found 770.4469.

EXAMPLE 22

Synthesis of de(3'-N-methyl)-3'-cyanomethyl-8, 9-anhydro-

pseudoerythromycin A 6, 9-hemiketal (EM742)



EM742

N,N-Diisopropylethylamine (320.9 μ L, 1.847 mmol) and bromoacetinitrile (128.3 μ L, 1.847 mmol) were added to dimethylformamide (3.1 mL) solution of EM703 (64.6 mg, 0.0921 mmol) at room temperature and stirred for 4 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM742 (53.1 mg, Yield: 78%, white powder).

EM742 : m. p. : 110-112 ℃.

IR (KBr) υ : 3485.5, 2973.7, 2935.1, 2863.8, 1702.8, 1456.0, 1382.7, 1319.1, 1265.1, 1166.7, 1126.2, 1074.2, 1037.5, 1016.3 cm^{-1}.

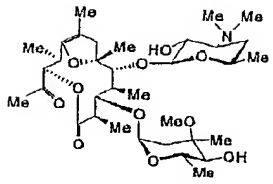
HRMS (FAB)m/z : $C_{38}H_{64}N_2O_{12}Na[M+Na]^+$

Calculated 763.4356

Found 763.4377.

REFERENTIAL EXAMPLE 2

Synthesis of de(12-hydroxy)-de[12-(1-hydroxypropyl)]-12-oxo-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM705)



EM705

Lead tetraacetate (508.0 mg, 1.136 mmol) was added to dichloromethane (24.0 ml) solution of EM701 (508.0 mg, 0.701 mmol) and stirred at room temperature for 40 minutes. After confirming completion of the reaction by TLC, the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01) to obtain EM705 (282.7 mg, Yield: 61%, white powder).

EM705 : m. p. : 108-112 ℃.

IR (KBr) υ : 3488, 2972, 2883, 1740, 1724, 1458, 1379, 1244, 1165, 1107, 1093, 1076, 1055, 1034, 1016 cm^{-1}.

HRMS (FAB) : $C_{34}H_{58}NO_{11}$ $[M+H]^+$

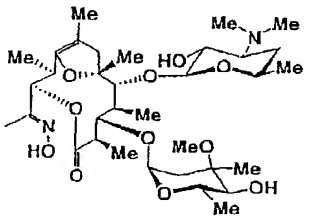
Calculated 656.4010

Found 656.4021.

EXAMPLE 23

Synthesis of de(12-hydroxy)-de[12-(1-hydroxypropyl)]-12

-hydroxyoxime-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM743) and the salt thereof



EM743

Pyridine (0.9 mL) was slowly added at 0℃ to ethanol (0.9 mL) solution of EM705 (116.5 mg, 0.1781 mmol) and hydroxylamine hydrochloride (32.0 mg, 0.533 mmol) and stirred for 3 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01 → 10 : 1 : 0.05) to obtain EM743 (114.5 mg, Yield: 96%, white powder).

EM743 : m. p. : 141-143 ℃.

IR (KBr) υ : 3485.8, 2971.8, 2937.1, 2883.1, 1737.5, 1459.8, 1378.9, 1255.4, 1247.7, 1166.7, 1112.7, 1089.6, 1076.1, 1037.5, 1014.4 cm^{-1}.

HRMS (FAB)m/z : $C_{34}H_{59}N_2O_{11}[M+H]^+$

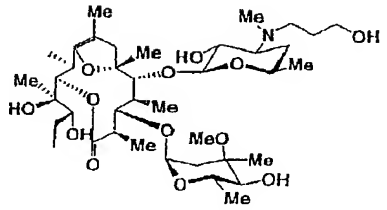
Calculated 671.4112

Found 671.4108.

EXAMPLE 24

Synthesis of de[(3'-N-methyl)-[3'-N-(3-hydroxy-1-propyl)]-8,

9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM744)



EM744

N,N-Diisopropylethylamine (338.3 μL, 1.942 mmol) and 3-bromo-1-propanol (175.6 μL, 1.942 mmol) were added to dimethylformamide (3.3 mL) solution of EM703 (68.1 mg, 0.0971 mmol) at room temperature and stirred for 48 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM744 (27.7 mg, Yield: 38%, white powder). The raw material EM703 was recovered 22.5 mg (Yield: 33%).

EM744 : m. p. : 142-145 ℃.

IR (KBr) υ : 3478.8, 2973.7, 2937.1, 2877.3, 1700.9, 1635.3, 1459.8, 1403.9, 1382.7, 1317.1, 1267.0, 1166.7, 1126.2, 1114.7, 1076.1, 1049.1, 1035.6, 1016.3 cm^{-1}.

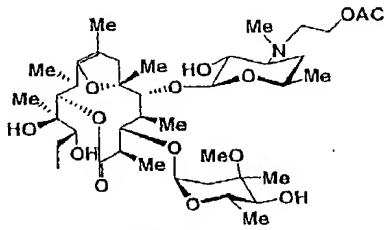
HRMS (FAB)m/z : $C_{39}H_{69}NO_{13}Na$ $[M+Na]^+$

Calculated 782.4666

Found 782.4667.

EXAMPLE 25

Synthesis of de(3'-N-methyl)-3'-N-(2-acetoxyethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM745)



EM745

N,N-Diisopropylethylamine (106.8 μL, 0.613 mmol) and 2-bromoethylacetate (67.6 μL, 0.613 mmol) were added to dimethylformamide (1.0 mL) solution of EM703 (21.5 mg, 0.0307 mmol) at room temperature and stirred for 48 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM745 (6.0 mg, Yield: 25%, white powder).

EM745 : m. p. : 131-133 ℃.

IR (KBr) υ : 3500.2, 3477.0, 2973.7, 2937.1, 2877.3, 1735.6, 1700.9, 1457.9, 1376.9, 1319.1, 1265.1, 1166.7, 1126.2, 1078.0, 1037.5, 1016.3 cm^{-1}.

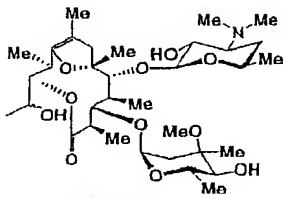
HRMS (FAB)m/z : $C_{40}H_{69}NO_{14}Na$ $[M+Na]^+$

Calculated 810.4615

Found 810.4629

EXAMPLE 26

Synthesis of de[12-(hydroxypropyl)]-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal (EM746)



EM746

Sodium borohydride (21.8 mg, 0,575 mmol) was added to methanol (2.9 mL) solution of EM705 (37.7 mg, 0.0575 mmol) at -78℃ and stirred for 30 minutes. Temperature of the reaction mixture was increased to 0℃ and further stirred for 30 minutes. After confirming completion of the reaction by TLC, the reaction was terminated by adding acetone (0.5 ml). The reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM746 (35.8 mg, Yield: 95%, white powder).

EM746 : m. p. : 116-118 ℃.

IR (KBr) υ : 3457.7, 2971.3, 2939.0, 1731.8, 1631.5, 1457.9, 1378.9, 1265.1, 1166.7, 1110.8, 1078.0, 1041.4, 1016.3 cm^{-1}.

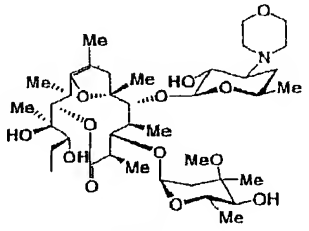
HRMS (FAB)m/z : $C_{34}H_{59}NO_{11}Na$ $[M+Na]^+$

Calculated 680.3963

Found 680.3963

EXAMPLE 27

Synthesis of de(3'-dimethylamino)-3'-morpholino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM747)



EM747

N,N-Diisopropylethylamine (45.8 μL, 0,263 mmol) and bis(2-bromoethyl) ether (33.1 μL, 0.263 mmol) were added in this order to acetinitrile (2.6 mL) solution of EM721 (18.1 mg, 0.0263 mmol) and stirred at 80℃ for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM747 (12.0 mg, Yield: 60%, white powder).

EM747 : m. p. : 139-142 ℃.

IR (KBr) υ : 3452.0, 2971.8, 2937.1, 2865.7, 1700.9, 1646.9, 1457.9, 1380.8, 1319.1, 1265.1, 1166.7, 1110.8, 1072.2, 1049.1, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{39}H_{67}NO_{13}Na$ $[M+Na]^+$

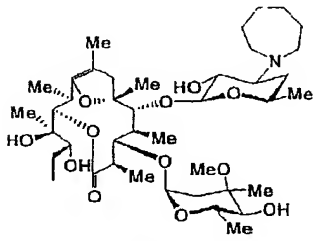
Calculated 780.4510

Found 780.4529

EXAMPLE 28

Synthesis of de(3'-dimethylamino)-3'-[hexahydro-1(1H)

-azepinyl]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM748)



EM748

N,N-Diisopropylethylamine (49.5 μL, 0,284 mmol) and 1,6-dibromohexane (43.6 μL, 0.284 mmol) were added in this order to acetinitrile (2.8 ml) solution of EM721 (19.5 mg, 0.0284 mmol) and stirred at 80℃ for 24 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM748 (11.7 mg, Yield: 54%, white powder).

EM748 : m. p. : 120-123 ℃.

IR (KBr) υ : 3430.7, 2971.8, 2933.2, 2858.0, 1708.6, 1629.6, 1457.9, 1378.9, 1319.1, 1263.1, 1166.7, 1112.7, 1083.8, 1047.2, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{41}H_{72}NO_{12}$ $[M+H]^+$

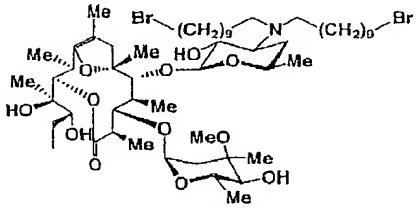
Calculated 770.5054

Found 770.5062.

EXAMPLE 29

Synthesis of bis-de(3'-N-methyl)-3', 3'-N, N-di-(10-bromo

-1-decanyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM749)



EM749

N,N-Diisopropylethylamine (45.6 μL, 0,262 mmol) and 1,10-dibromodecane (58.9 μL, 0.262 mmol) were added in this order to acetinitrile (2.6 mL) solution of EM721 (18.0 mg, 0.0262 mmol) and refluxed at 80℃ for 36 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 20 : 1 : 0.1) to obtain EM749 (14.9 mg, Yield: 51%, white powder).

EM749 : m. p. : 132-134 ℃.

IR (KBr) υ : 3448.1, 2929.3, 1700.9, 1629.6, 1459.8, 1375.0, 1319.1, 1267.0, 1166.7, 1126.2, 1081.9, 1049.1, 1016.3 cm^{-1}.

HRMS (FAB)m/z : $C_{55}H_{100}NO_{12}Br_2$ $[M+H]^+$

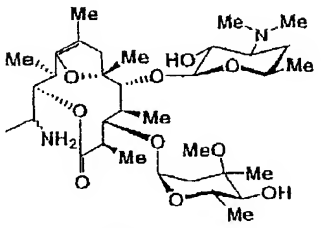
Calculated 1126

Found 1126.

EXAMPLE 30

Synthesis of de(12-hydroxy)-de[12-(hydroxypropyl)]-12

-amino-8,9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM750)



EM750

Molybdenum oxide (IV) (10.0 mg, 0,0694 mmol) and sodium borohydride (10.5 mg, 0.277 mmol) were added to ethanol (2.3 mL) solution of EM743 (15.5 mg, 0.0231 mmol) at 0℃ and stirred for 4 hours. After confirming completion of the reaction by TLC, the reaction was terminated by adding acetone (0.5 mL), and the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 1 : 0.1) to obtain EM750 (13.4 mg, Yield: 88%, white powder).

EM750 : m. p. : 104-107 ℃.

IR (KBr) υ : 3448.1, 2971.8, 2935.1, 1729.8, 1629.6, 1457.9, 1378.9, 1259.3, 1166.7, 1114.7, 1078.0, 1039.4, 1016.3 cm^{-1}.

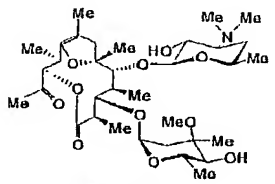
HRMS (FAB)m/z : $C_{34}H_{60}N_2O_{10}Na$ $[M+Na]^+$

Calculated 679.4145

Found 679.4117.

REFERENTIAL EXAMPLE 3

Synthesis of de(3'-N-methyl)-de(12-hydroxy)-de-[12-(1-hydroxy propyl)]-12-oxo-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM706)



EM706

Lead tetraacetate (508.0 mg, 1.136 mmol) was added to dichloromethane (24.0 ml) solution of EM701 (508.0 mg, 0.701 mmol) and stirred at room temperature for 40 minutes. After confirming completion of the reaction by TLC, the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 10 : 0.5 : 0.01) to obtain EM706 (71.6 mg, Yield: 16%, white powder).

EM706 : m. p. : 176-179 ℃.

IR (KBr) υ : 3468, 2966, 2852, 2360, 1736, 1718, 1558, 1462, 1379, 1246, 1165, 1126, 1099, 1076, 1038, 1016 cm^{-1}.

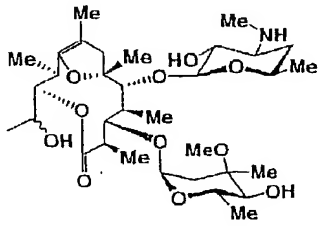
HRMS (FAB)m/z : $C_{33}H_{56}NO_{11}[M+H]^+$

Calculated 642.3853

Found 642.3866.

EXAMPLE 31

Synthesis of de(3'-N-methyl)-de[12-(1-hydroxypropyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal (EM751)



EM751

Sodium borohydride (22.9 mg, 0.605 mmol) was added to methanol (3.0 mL) solution of EM706 (38.8 mg, 0.0605 mmol) at 0℃ and stirred for 1 hour. After confirming completion of the reaction by TLC, the reaction was terminated by adding acetone (0.5 mL), and the reaction mixture was diluted with saturated brine-aqueous saturated sodium hydrogen carbonate (1:1, v/v) and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM751 (31.4 mg, Yield: 81%, white powder).

EM751 : m. p. : 123-125 ℃.

IR (KBr) υ : 3504.0, 2448.1, 2971.8, 2935.1, 1729.8, 1664.3,1594.8, 1457.9, 1378.9, 1334.1, 1265.1, 1166.7, 1126.2, 1078.0, 1041.4, 1016 cm^{-1}.

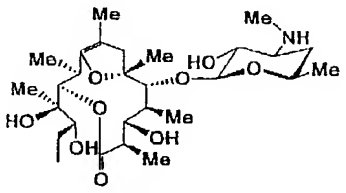
HRMS (FAB)m/z : $C_{33}H_{58}NO_{11}[M+H]^+$

Calculated 644.3987

Found 644.4011

EXAMPLE 32

Synthesis of de(3-O-cladinosyl)-de(3'-N-methyl)-8,9-anhydrous -pseudoerythromycin A 6, 9-hemiketal (EM754)



EM754

p-toluenesulfonic acid monohydrate (53.9 mg, 0.283 mmol) was added to dimethylformamide (3.8 mL) solution of EM703 (132.4 mg, 0.189 mmol) and stirred at 50℃ for 6 hours. After confirming completion of the reaction by TLC, the reaction mixture was diluted with water, adjusted to pH 8 by adding saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The organic layer was dehydrated by adding sodium sulfate, filtered to remove the sodium sulfate, and removed the solvent to obtain crude substance. The crude substance was purified by silica gel column chromatography (chloroform : methanol : aqueous ammonia = 15 : 1 : 0.1) to obtain EM754 (50.2 mg, Yield: 49%, white powder).

EM754 : m. p. : 218-221 ℃.

IR (KBr) υ : 3432.7, 2969.8, 2927.4, 2858.0, 1708.6, 1629.6, 1457.9, 1405.9, 1380.8, 1319.1, 1270.9, 1232.3, 1130.1, 1078.0, 1039.4 cm^{-1}.

HRMS (FAB)m/z : $C_{28}H_{49}NO_9Na$ $[M+Na]^+$

Calculated 566.3305

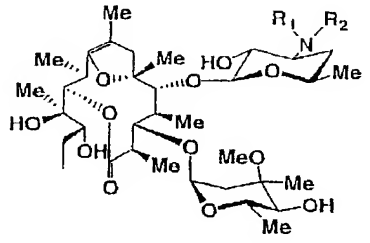
Found 566.3311.

Effect of the Invention

Novel pseudoerythromycin of the present invention has decreased antibacterial activity and increased antiinflammatory action, and is expected as the novel antiinflammatory agent.

Claims

1. A novel pseudoerythromycin derivative represented by the general formula [I],



[I]

wherein R_1 and R_2 are same or different and each represents H, alkyl, alkynyl, acyl, or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.

2. A compound according to claim 1 which is de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

3. A compound according to claim 1 which is de(3'-N-methyl)-3' -N-sulfonyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

4. A compound according to claim 1 which is de(3'-N-methyl)-[3'-N-(3-hydroxy-1-propyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

5. A compound according to claim 1 which is de(3'-N-methyl) -3'-N-(2-acetoxyethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

6. A compound according to claim 1 which is de(3'-N-methyl)-3'-N

-cyanomethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

7. A compound according to claim 1 which is de(3'-N-methyl)-3'-N-(2-fluoroethyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

8. A compound according to claim 1 which is bis-de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

9. A compound according to claim 1 which is bis-de(3'-N-methyl)-3'-N-ethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

10. A compound according to claim 1 which is bis-de(3'-N-methyl)-3', 3'-N, N-diethyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

11. A compound according to claim 1 which is bis-de(3'-N-methyl)-3'-N-allyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

12. A compound according to claim 1 which is bis-de(3'-N-methyl)-3', 3'-N, N-diallyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

13. A compound according to claim 1 which is bis-de(3'-N-methyl)-3'-N-propargyl-8, 9-anhydro-pseudoerythromycin A 6, 9-

hemiketal or salt thereof.

14. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-dipropargyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

15. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-propyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

16 A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-dipropyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

17 A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-hexyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

18. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-dihexyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

19. A compound according to claim 1 which is bis-de(3'-N-methyl) -3'-N-benzyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

20. A compound according to claim 1 which is bis-de(3'-N-methyl) -3', 3'-N, N-dibenzyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

21. A compound according to claim 1 which is bis-de(3'-N-methyl)-3'-N-(2-propyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

22. A compound according to claim 1 which is bis-de(3'-N-methyl)-3', 3'-N, N-di-(10-bromo-1-decanyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

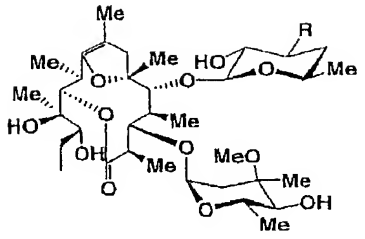
23. A compound according to claim 1 which is bis-de(3'-N-methyl)-3'-N-acetyl-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

24. The derivative according to claim 1 wherein the compound represented by the general formula [I] has promoting action for differentiation-induction from monocyte to macrophage.

25. The derivative according to claim 1 wherein the compound represented by the general formula [I] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

26. The derivative according to claim 1 wherein the compound represented by the general formula [I] has suppressive effect against pneumonia caused by influenza viral infection.

27. A novel pseudoerythromycin derivative represented by the general formula [II],



[II]

whrein R is heterocyclic containing N which may optionally have substituents, and Me indicates methyl.

28. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-piperidino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

29. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-pyrrolidino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

30. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-morpholino-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

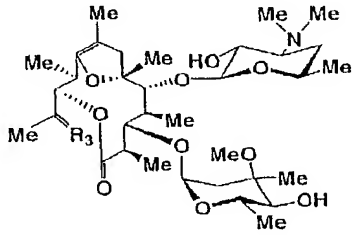
31. A compound according to claim 27 which is de(3'-dimethyl amino)-3'-[hexahydro-1(1H)-azepinyl)-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

32. The derivative according to claim 27 wherein the compound represented by the general formula [II] has promoting action for differentiation-induction from monocyte to macrophage.

33. The derivative according to claim 27 wherein the compound represented by the general formula [II] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

34. The derivative according to claim 27 wherein the compound represented by the general formula [II] has suppressive effect against pneumonia caused by influenza viral infection.

35. A novel pseudoerythromycin derivative represented by the general formula [III],



[III]

wherein R_3 is O or NOH, and Me indicates methyl.

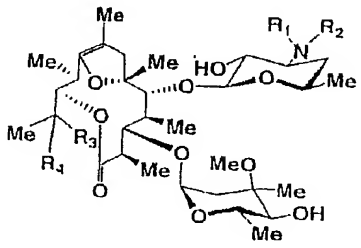
36. A compound according to claim 35 which is de(12-hydroxy)-de[12-(1-hydroxypropyl)]-12-hydroxyoxime-8,9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

37. The derivative according to claim 35 wherein the compound represented by the general formula [III] has promoting action for differentiation-induction from monocyte to macrophage.

38. The derivative according to claim 35 wherein the compound represented by the general formula [III] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

39. The derivative according to claim 35 wherein the compound represented by the general formula [III] has suppressive effect against pneumonia caused by influenza viral infection.

40. A novel pseudoerythromycin derivative represented by the general formula [IV],



[IV]

whereiin R_1 and R_2 are same or different and each represents H or methyl, R_3 and R_4 represent H, hydroxyl or amino, and Me indicates methyl.

41. A compound according to claim 40 which is de[12-(1-hydroxy propyl)]-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

42. A compound according to claim 40 which is de(12-hydroxy) -de[12-(1-hydroxypropyl)]-12-amino-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

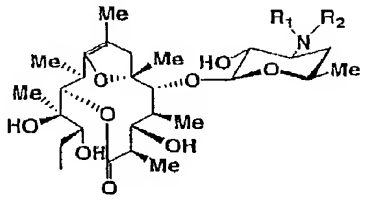
43. A compound according to claim 40 which is de(3'-N-methyl)-de [12-(1-hydroxypropyl)]-8, 9-anhydro-pseudo erythromycin A 6, 9-hemiketal or salt thereof.

44. The derivative according to claim 40 wherein the compound represented by the general formula [IV] has promoting action for differentiation-induction from monocyte to macrophage.

45. The derivative according to claim 40 wherein the compound represented by the general formula [IV] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

46. The derivative according to claim 40 wherein the compound represented by the general formula [IV] has suppressive effect against pneumonia caused by influenza viral infection.

47. A novel pseudoerythromycin derivative represented by the general formula [V],



[V]

wherein R_1 and R_2 are same or different and each represents H or methyl, and Me indicates methyl.

48. A compound according to claim 47 which is de(3-O-cladinosyl)-8, 9-anhydro-pseudoerythromycin A 6, 9-hemiketal or salt thereof.

49. A compound according to claim 47 which is de(3-O-cladinosyl)-de(3'-N-methyl)-8, 9-anhydro-pseudoerythromycin A

6, 9-hemiketal or salt thereof.

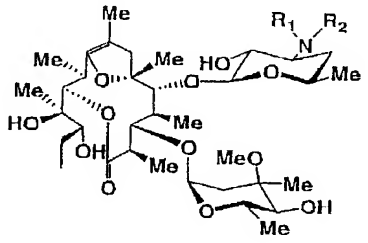
50. The derivative according to claim 47 wherein the compound represented by the general formula [V] has promoting action for differentiation-induction from monocyte to macrophage.

51. The derivative according to claim 47 wherein the compound represented by the general formula [V] has a suppressive effect against bleomycin-induced pulmonary fibrosis.

52. The derivative according to claim 47 wherein the compound represented by the general formula [V] has suppressive effect against pneumonia caused by influenza viral infection.

ABSTRACT

The present invention is to obtain novel anti-inflammatory agents having decreased antibacterial activity and increased anti-inflammatory action, and is psedoerythromycin derivatives represented by the following general formula [I],



[I]

wherein R1 and R2 are same or different and each represents H, alkyl, alkynyl, acyl or sulfonyl, in which these groups may optionally have substituents, and Me indicates methyl.

FIG. 1

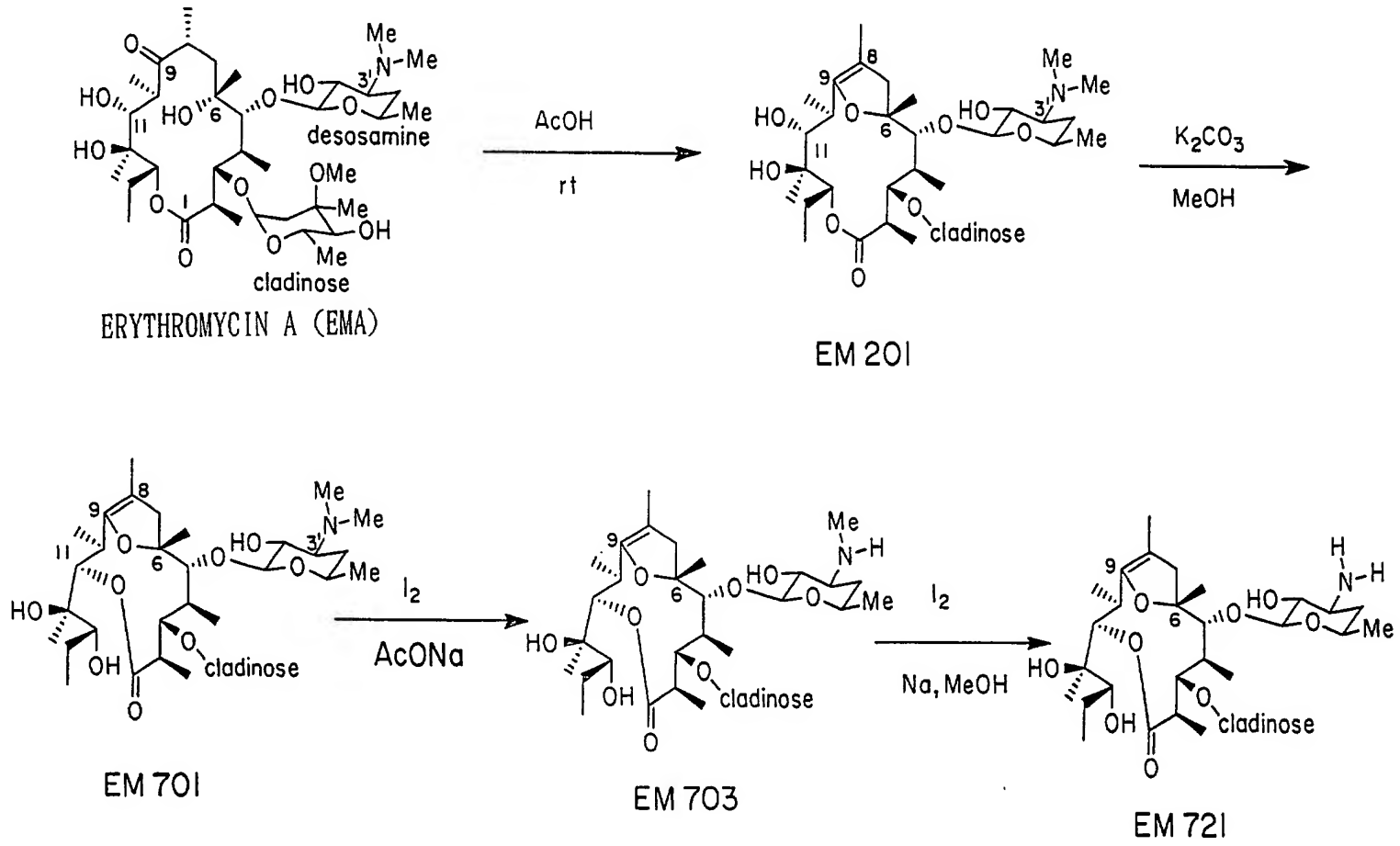


FIG. 2

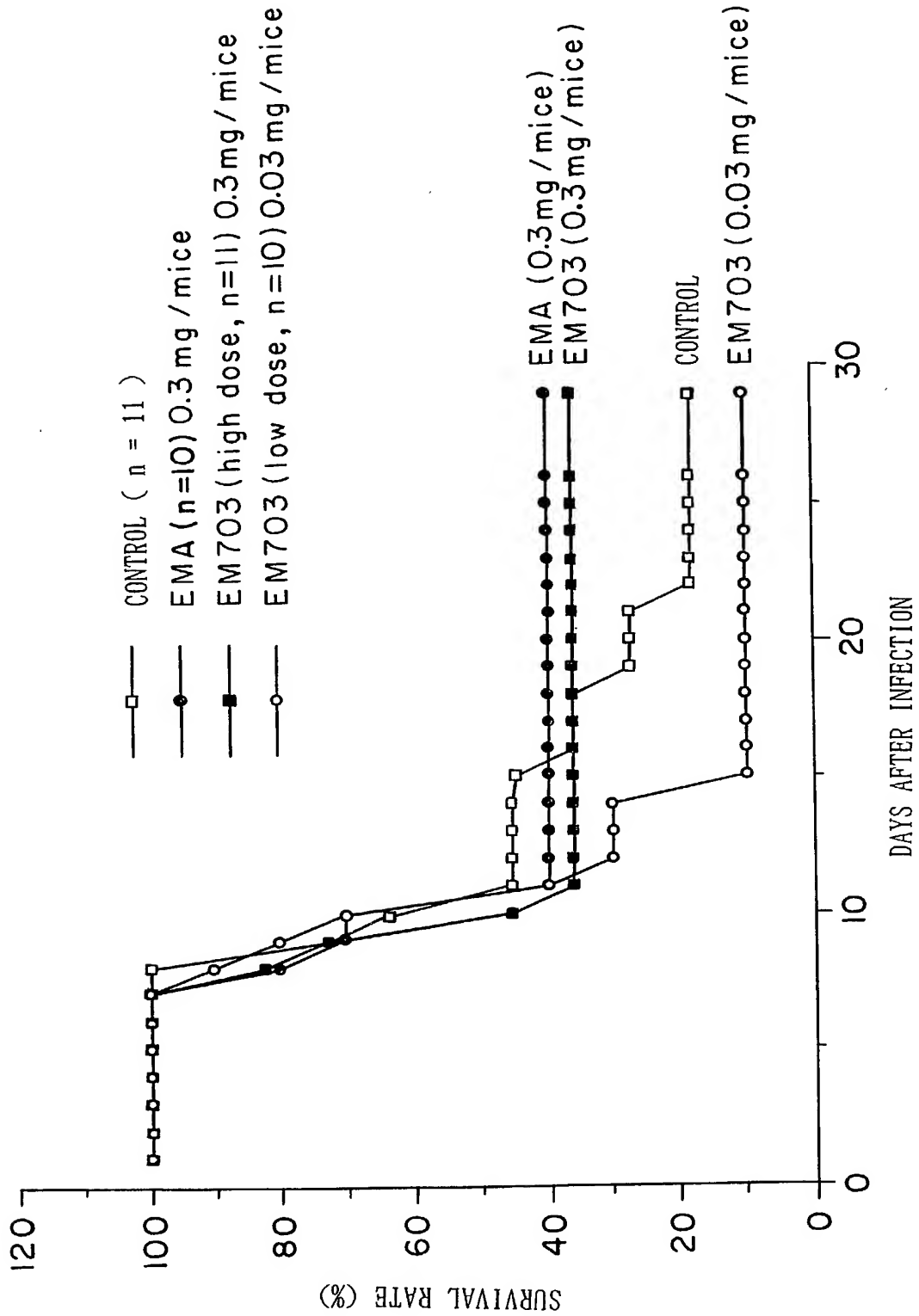
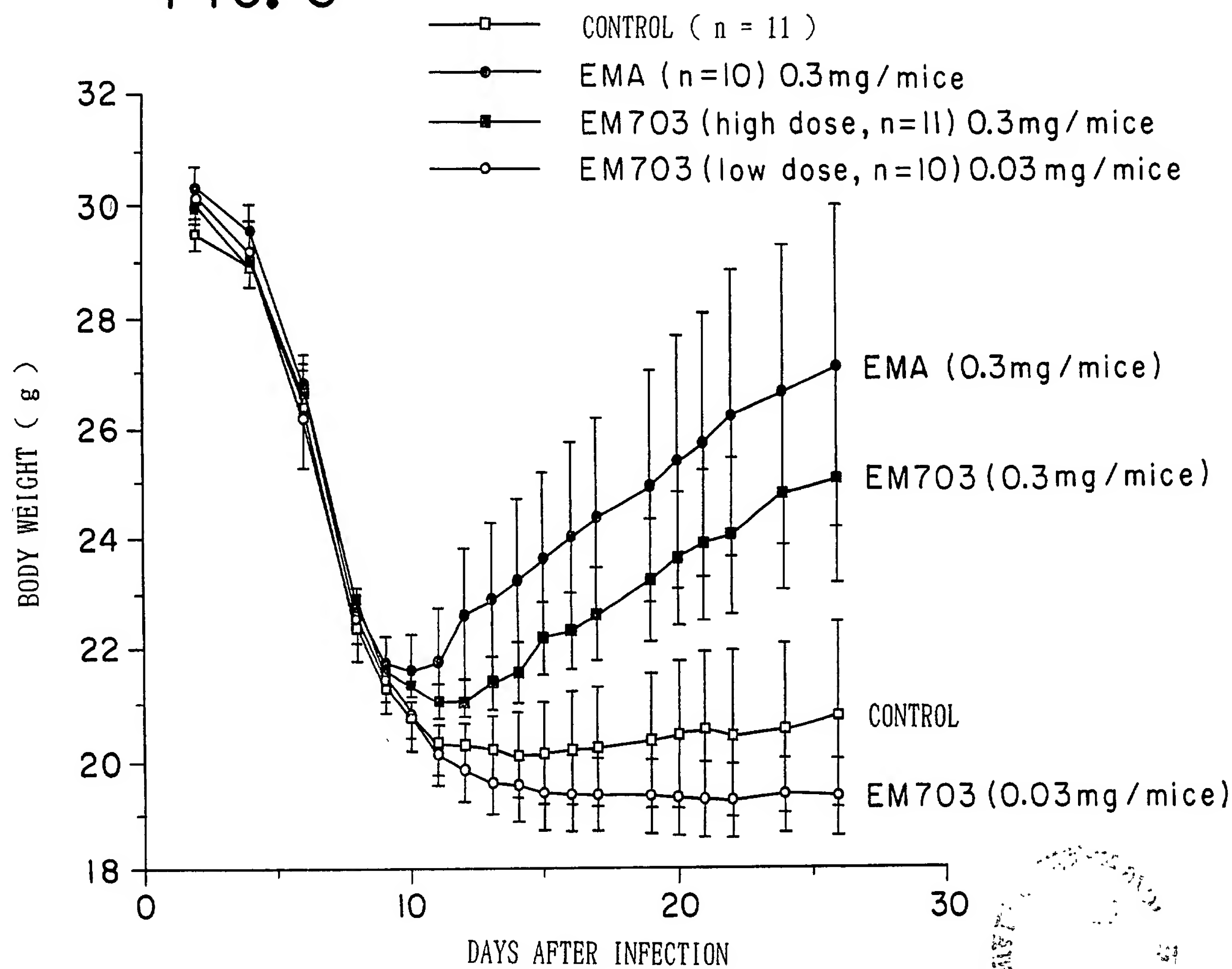

CONTROL (n = 11)
EMA (n=10) 0.3 mg / mice
EM703 (high dose, n=11) 0.3mg / mice
EM703 (low dose, n=10) 0.03 mg / mice
EMA (0.3mg / mice)
EM703 (0.3mg / mice)
CONTROL
EM703 (0.03mg / mice)
SURVIVAL RATE (%)
120
100
80
60
40
20
0
0
10
20
30
DAYS AFTER INFECTION

FIG. 3



COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: NOVEL PSEUDOERYTHROMYCIN DERIVATIVES

the specification of which: *(check one)*

REGULAR OR DESIGN APPLICATION

☐ is attached hereto.

☒ was filed on March 22, 2002 as application Serial No. _____

and was amended on _____ (if applicable).

PCT FILED APPLICATION ENTERING NATIONAL STAGE

☒ was described and claimed in International application No. PCT/JP00/05503 filed on August 17, 2000 and as amended on _____(if any).

I hereby state that I have reviewed and understand the contents of the above-identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

PRIORITY CLAIM

I hereby claim foreign priority benefits under 35 USC 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of the application on which priority is claimed.

PRIOR FOREIGN APPLICATION(S)

Country	Application Number	Date of Filing (day, month, year)	Priority Claimed
JAPAN	PCT/JP00/05503	17/8/2000	YES

I hereby claim the benefit under Title 35, United States Code §119(e) of any United States provisional patent application(s) listed below:

Application No. Filing Date Status (patented, pending abandoned)

(Complete this part only if this is a continuing application.)

I hereby claim the benefit under 35 USC 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 USC 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37 Code of Federal Regulations §1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application No. Filing Date Status (patented, pending abandoned)

10089965 .072502

Docket No. 8012-1018

POWER OF ATTORNEY

The undersigned hereby authorizes the U.S. attorney or agent named herein to accept and follow instructions from **KYORITSU INSTITUTE FOR INTERNATIONAL INDUSTRIAL PROPERTY** as to any action to be taken in the Patent and Trademark Office regarding this application without direct communication between the U.S. attorney or agent and the undersigned. In the event of a change in the persons from whom instructions may be taken, the U.S. attorney or agent named herein will be so notified by the undersigned.

As a named inventor, I hereby appoint the registered patent attorneys represented by Customer No. **000466** to prosecute this application and transact all business in the Patent and Trademark Office connected therewith, including: **Robert J. PATCH, Reg. No. 17,355, Andrew J. PATCH, Reg. No. 32,925, Robert F. HARGEST, Reg. No. 25,590, Benoît CASTEL, Reg. No. 35,041, Thomas W. PERKINS, Reg. No. 33,027, Roland E. LONG, Jr., Reg. No. 41,949, and Eric JENSEN, Reg. No. 37,855,**

c/o YOUNG & THOMPSON,
Second Floor,
745 South 23rd Street,
Arlington, Virginia 22202.

00466
PATENT TRADEMARK OFFICE

Address all telephone calls to Young & Thompson at 703/521-2297. Telefax: 703/685-0573.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

1-00

Full name of sole or first inventor: Satoshi OMURA

Inventor's signature: Satoshi Omura Date: Apr. 23, 2002

Residence: Tokyo, JAPAN JPX Citizenship: JAPAN

Post Office Address: c/o The Kitasato Institute, 9-1, Shirokane 5-chome, Minato-ku, Tokyo, 108-8642 JAPAN

2-00

Full name of second joint inventor, if any: Yuzuru IWAI

Inventor's signature: Yuzuru Iwai Date: Apr. 17, 2002

Residence: Tokyo, JAPAN JPX Citizenship: JAPAN

Post Office Address: c/o The Kitasato Institute, 9-1, Shirokane 5-chome, Minato-ku, Tokyo, 108-8642 JAPAN

3-00

Full name of third joint inventor, if any: Toshiaki SUNAZUKA

Inventor's signature: Toshiaki Sunazuka Date: April 22, 2002

Residence: Tokyo, JAPAN JPX Citizenship: JAPAN

Post Office Address: c/o The Kitasato Institute, 9-1, Shirokane 5-chome, Minato-ku, Tokyo, 108-8642 JAPAN

4-00

Full name of fourth joint inventor, if any: Tohru NAGAMITSU

Inventor's signature: Tohru Nagamitsu Date: April 15, 2002

Residence: Tokyo, JAPAN JPX Citizenship: JAPAN

Post Office Address: c/o The Kitasato Institute, 9-1, Shirokane 5-chome, Minato-ku, Tokyo, 108-8642 JAPAN